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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/707,041	08/06/97	GREENBERGER	7033/103

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EXAMINER
CHEN, S

ART UNIT	PAPER NUMBER
1633	13

DATE MAILED: 03/17/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/907,041	Applicant(s) Joel S. Greenberger
	Examiner Shin-Lin Chen	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-31 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 12

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application is a file wrapper continuation of Application No. 08/484,836 filed on 6-7-95, abandoned on 8-6-97. A preliminary amendment was entered on 8-6-97. Application No. 08/484,836 is a continuation of parent application 08/136,079, filed 10-15-93, issued as US Patent No. 5,599,712.

This application repeats a substantial portion of prior Application No. 08/136,079, filed 10-15-93, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

> It does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. 120 which discloses and claims subject matter in addition to that disclosed in the prior copending application, acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

The date recited as filing date under 35 U.S.C. 120, is "10-15-95", a correct oath or declaration must be submitted by the applicant.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 5,599,712(A). Although the conflicting claims are not identical, they are not patentably distinct from each other because, although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 27-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Heckl et al., 1993 (B).

Claims 27-29 are drawn to pharmaceutical composition comprising a polynucleotide, in a pharmaceutically acceptable vehicle, encoding a protein capable of neutralizing or eliminating free radicals, superoxide anions, and heavy metals in a subject. Heckl et al. disclose a cloned gene encoding human manganese superoxide dismutase (hMn-SOD) and teaches transformation of prokaryote and mammalian cells using plasmid and viral vector, respectively, to express hMn-SOD protein. Therefore, claims 27-29 are rejected under 35 U.S.C. 102(e).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-27, and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-27, and 29-31 encompass a method for protecting a subject against an agent that elicits free radicals, superoxide anions, or heavy metal cations, said method comprising the steps of administering to said subject in vivo a pharmaceutical composition comprising a polynucleotide that encodes a protein transiently expressed in said subject, and a pharmaceutically acceptable vehicle for said polynucleotide; a pharmaceutical composition comprising said polynucleotide in a pharmaceutically acceptable vehicle. The specification discloses the construction of recombinant adenoviral vectors Ad-MT, Ad-MnSOD, and Ad-γ-GTP; the expression of metallothionein (MT), manganese superoxide dismutase (MnSOD), and γ-Glutamyltranspeptidase (γ-GTP) in rat lung epithelium in vivo, and the function assay for MT, MnSOD, and γ-GTP proteins. The specification discloses expression of greater levels of γ-GTP in murine melanoma cell line B16 renders the cell line less sensitive to γ-irradiation, and expression of a MnSOD transgene under control of the irradiation inducible egr-1 promoter increases the radioresistance of 32D CL 3 hematopoietic progenitor cells *in vitro*.

The specification does not disclose any data to demonstrate that MT, MnSOD, or γ-GTP has therapeutic effect to the subject *in vivo*. The specification does not disclose in vitro and in vivo data to demonstrate that any protein other than MT, SOD and γ-GTP can neutralize or eliminate free radicals, superoxide anions, and heavy metal cations when transiently expressed in a subject. The specification does not teach how to make and use a vector containing any

transgene which encodes a protein other than MT, SOD and γ-GTP capable of neutralizing or eliminating toxic species, i.e. free radicals, superoxide anions, heavy metal cations. There is no working example of protecting any subject, e.g. a mammal, insect, fish, arthropod, ants, plants, *in vivo* from said toxic species by using said method set forth above. Different subject may differ dramatically physiologically, pathologically and can react to said toxic species differently, and the mechanism of neutralizing said toxic species can vary dramatically from species to species. Furthermore, said toxic species might be undesirable and toxic in some species but it might be beneficial and desirable in other species. The specification indicates that protection from radiation provided by recombinant DNA expressing γ-GTP enzyme can differ from cell-line to cell-line. Unlike the murine melanoma cell line B16, human A549 carcinoma cell line and human IB3-1 cell line were not protected by increased levels of γ-GTP activity in transfected cells. Therefore, it is likely that increased levels of γ-GTP, MT, MnSOD, or other proteins which can neutralize or eliminate said toxic species *in vitro* may not provide protection for a subject from said toxic species *in vivo*. This is even more likely to be true considering the species which differs from each other dramatically, physiologically and pathologically.

The state of the art of gene therapy was unpredictable at the time of the invention. Mastrangelo et al. 1996 (U) teaches what is critical of the success of gene therapy is the efficient transfer of a functioning gene to the target cell. This has proven a major stumbling block, particularly for in vivo gene transfer (eg. page 10, left column, first paragraph). Gene transfer efficiency aside, none of the replicating vectors seem ready for systemic use clinically. Only

liposome is ready for this application and their usefulness will be severely impaired by limited access to tumor sites, degradation in plasma and clearance by the reticuloendothelial system (page 12, first paragraph).

Orkin et al. 1995 (V) reported that none of the available vector systems for gene transfer is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Retrovirus infects and integrates only dividing cells, other problems include cumbersome preparation and relatively low titer, size constraints on inserted genes, and the potential for genetic damage due to random integration in the host genome. Adenovirus, Herpesvirus and poxvirus all have the problem of relatively high immunogenicity and complexity of its genome. Adeno-associated virus requires replicating adenovirus to grow and no helper cell line available. Direct administration of DNA or DNA complexes (e.g., liposomes) has disadvantages of lower efficiency of gene transfer (compared with viruses) and the absence of mechanisms for specifically maintaining the introduced DNA within the cell.

The specification fails to provide adequate guidance for a method to protect a mammal, insect, fish, arthropod, ants, or plant etc. from said toxic species by using any kind of vector other than adenovirus, any kind of promoter other than egr-1 to transiently express any polynucleotide that encodes a protein and achieve therapeutic effect *in vivo*. Different inducible transcriptional regulatory sequence may behave differently in various species or subject in vivo, an adequate guidance is required to enable the full scope of the invention. In addition to the uncertainties of

the therapeutic effect in vitro and in vivo in different subject, there is also the uncertainties offered by different promoter, different protein and different vector used in said method for a therapeutic effect in a subject.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the claimed inventions. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-8, 12-15, 19-26, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al., 1994 (N) in view of Wegner et al., 1994 (O).

Brown et al. teaches the use of a transgene comprising a nucleotide sequence encoding a SOD polypeptide for treatment of a patient with neurodegenerative disease, e.g. Amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, with neoplasia, or with deleterious mutation in the SOD gene, nitric oxide synthase-encoding gene, glutathione peroxidase-encoding

gene to restore the normal function of SOD polypeptide, i.e. eliminate certain oxygen free radicals, e.g. superoxide. Brown et al. also teaches the use of retroviral vector for gene transfer of SOD1, SOD2, or SOD3 genes which encode therapeutic SOD polypeptides, and insertion of SOD coding sequences into genomic DNA of the patient under the control of the wild type promoter by microinjection. Brown et al. does not teach exposing the subject in an agent which elicits production of a toxic species. Wegner et al., teaches a method for inhibiting pulmonary oxygen toxicity in a patient requiring elevated levels of oxygen by prophylactic topical administration, e.g. intranasal insufflation, inhalation, intratracheal instillation, of human MnSOD in tetrameric form and shows the protection of baboon lung from elevated levels of oxygen. Therefore, it would have been obvious for a person of ordinary skill at the time of the invention to protect a subject by expressing a protein capable of neutralizing or eliminating toxic species produced by an agent which said subject is exposed to with a reasonable expectation of success. Thus, claims 1-8, 12-15, 19-26, 30 and 31 are rejected under 35 U.S.C.103(a).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton can be reached on (703) 308-2801. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800